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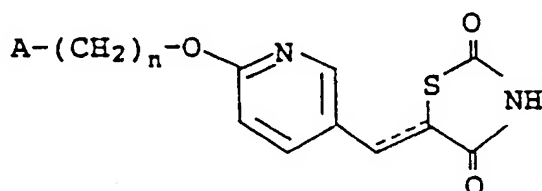
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Sevenoaks, Kent TN13 1XR (GB)**(54) **Thiazolidinedione derivatives, their production and use.**

(57) The object of the present invention is to provide a new thiazolidinedione derivative exhibiting excellent hypoglycemic and hypolipidemic action. Novel thiazolidinedione derivatives represented by the general formula (I):



(I)

wherein n represents an integer of from 1 to 3; A represents an aromatic 5-membered heterocyclic ring residue which has at least one nitrogen atom as a ring component atom and which may be substituted; said residue A being bound within the said alkoxy group $[A-(CH_2)_n-O-]$ via a carbon atom adjacent to a nitrogen atom of said residue, and is a single bond or a double bond,

and novel pharmacologically acceptable salts thereof,
show excellent hypoglycemic and hypolipidemic actions, and are also effective against hypertension.

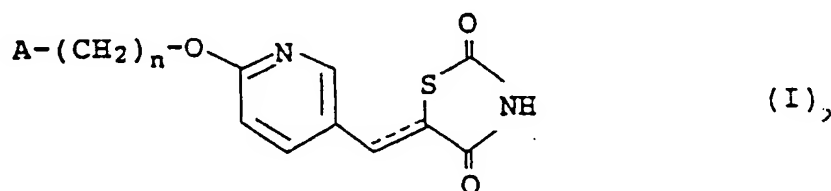
The present invention relates to a new thiazolidinedione derivative or its pharmaceutically acceptable salt possessing hypoglycemic or hypolipidemic activity to medicaments specifically a diabetic medicament, containing the said derivative or salt thereof and to the pharmaceutical use of said derivative or salt and of said medicament.

Traditionally, various biguanide compounds and sulfonylurea compounds have been used as diabetic remedies. However, biguanide compounds are hardly used at present, since they cause lactic acidosis, while sulfonylurea compounds, with their potent hypoglycemic action, often cause severe hypoglycemia, requiring special attention in use. There are, however, thiazolidinedione derivatives which are known to possess hypoglycemic and hypolipidemic activity and are also free of such drawbacks. One example is Japanese Patent Examined Publication No. 57635/1987, which describes a series of 5-[2-alkoxy-5-pyridyl)methyl]-2,4-thiazolidinedione derivatives having a (substituted-3-pyridyl)-methyl group at its 5-position.

We have investigated 5-[(substituted-3-pyridyl)methyl]-2,4-thiazolidinedione derivatives possessing potent hypoglycemic and hypolipidemic activity, and have found that their activity is markedly enhanced by the introduction into the pyridine ring thereof of an alkoxy group having thereon an aromatic 5-membered heterocyclic ring residue which contains at least one nitrogen atom as a ring component atom, and which binds via a carbon atom adjacent to a nitrogen atom of the ring residue.

Accordingly, the present invention comprises:

(1) thiazolidinedione derivatives represented by the general formula:

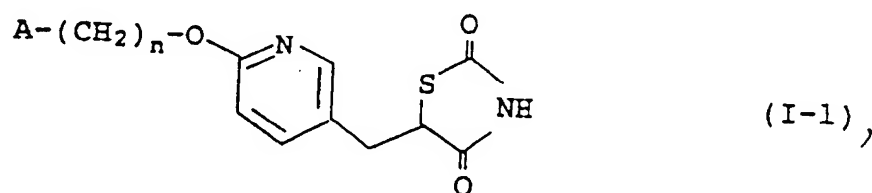


wherein n represents an integer of from 1 to 3; A represents an aromatic 5-membered heterocyclic ring residue which has at least one nitrogen atom as a ring component atom and which may be substituted, said residue (A) being bound within the alkoxy group $[\text{A}-(\text{CH}_2)_n-\text{O}-]$ via a carbon atom adjacent to a nitrogen atom of the ring residue; and

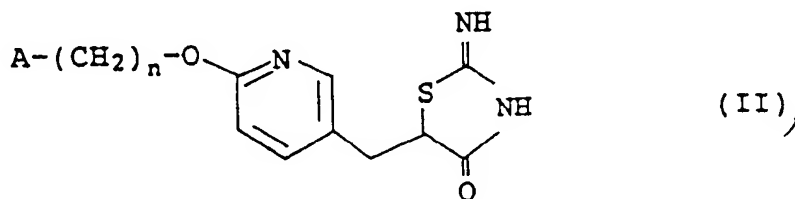
..... is a single bond or a double bond, and pharmacologically acceptable salts thereof;

(2) a pharmaceutical composition containing, as an active ingredient, a thiazolidinedione derivative represented by the general formula (I) as defined above, or a pharmacologically acceptable salt thereof;

(3) a method of producing a thiazolidinedione derivative represented by the general formula (I-1):



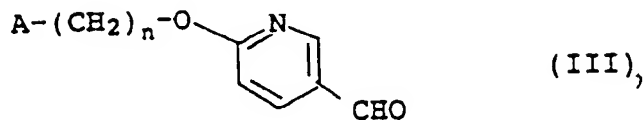
wherein the symbols n and A in said formula (I-1) have the same meaning as are given above in connection with said formula (I), characterized by the hydrolysis of an iminothiazolidinone compound represented by the general formula (II):



wherein the symbols n and A in said formula (II) have the same meanings as are given above; and

(4) a method of producing a thiazolidinedione derivative represented by the general formula (I) as defined

above, characterised by the condensation with 2,4-thiazolidinedione of a compound represented by the general formula (III):

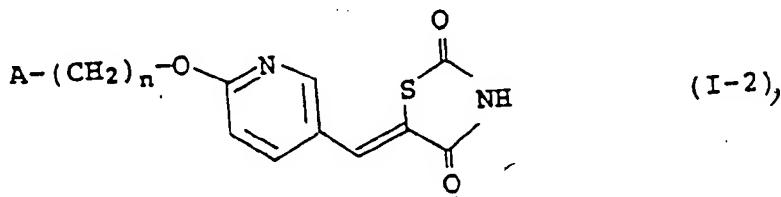


10 wherein the symbols n and A in said formula (III) have the same meanings as are given above in connection with said formula (I),

and, if necessary or desirable, reducing the resulting compound.

With respect to the above general formulae (I), (I-1), (II) and (III), n may vary from 1 to 3, but is preferably the integer 2 or 3.

15 The compound represented by the general formula (I) wherein the symbol is a single bond is specifically represented by the general formula (I-1), and the compound represented by the general formula (I) wherein the symbol is a double bond is specifically represented by the general formula (I-2), as follows:



wherein the symbols n and A in said formula (I-2) have the same meanings as are given above in connection with formula (I).

As regards compounds of the general formula (I), those having a single bond at the moiety indicated by in the general formula (I) are preferred.

With respect to the above general formulae (I-1), (I-2), (II) and (III), the aromatic 5-membered heterocyclic ring residue for A is defined as follows:

- 35
- (1) It is a 5-membered ring.
 - (2) It is an heterocyclic ring having at least one nitrogen atom as a ring component atom.
 - (3) It may have two or more nitrogen atoms, and may also have hetero atoms other than nitrogen, e.g., oxygen and/or sulfur, as ring component atoms.
 - (4) The ring is an aromatic ring having an unsaturated bond.
 - (5) It is a ring bound within the alkoxy group via a carbon atom of said ring adjacent to a nitrogen atom thereof.
 - (6) It may be substituted at any position on the ring.

The aromatic 5-membered heterocyclic ring residue (A) is exemplified by pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (2-imidazolyl; 4-imidazolyl), triazolyl(1,2,3-triazol-4-yl,1,2,4-triazol-3-yl), tetrazolyl, oxazolyl (2-oxazolyl,4-oxazolyl) and thiazolyl(2-thiazolyl,4-thiazolyl).

40 This aromatic 5-membered heterocyclic ring residue may have one or more substituents at any positions on the ring. Such substituents are exemplified by hydrocarbon residues and heterocyclic ring residues, which may have their own substituents.

Such hydrocarbon residues include aliphatic hydrocarbon residues, alicyclic hydrocarbon residues, aliphatic-aliphatic hydrocarbon residues, aryl-aliphatic hydrocarbon residues and aromatic hydrocarbon residues. Such aliphatic hydrocarbon residues include those having 1 to 8 carbon atoms, specifically, saturated aliphatic hydrocarbon residues having 1 to 8 carbon atoms, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl or octyl, and unsaturated aliphatic hydrocarbon residues having 2 to 8 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-buty-
50 tynyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 1-hexynyl, 3-hexynyl, 2,4-hexadi-
nyl, 5-hexynyl, 1-heptylnyl and 1-octynyl. Such alicyclic hydrocarbon residues include those having 3 to 7 carbon atoms, specifically, saturated alicyclic hydrocarbon residues having 3 to 7 carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and unsaturated alicyclic hydrocarbon residues having 5
55 to 7 carbon atoms, e.g., 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl. Such alicyclic aliphatic hydrocarbon residues include those resulting from the binding of the above-mentioned alicyclic hydro-

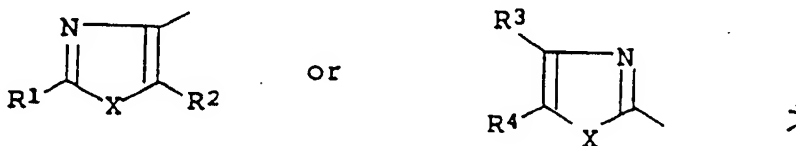
carbon residues and above-mentioned aliphatic hydrocarbon residues to have 4 to 9 carbon atoms, e.g., cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl. Such aryl-aliphatic hydrocarbon residues include phenylalkyls having 7 to 9 carbon atoms, e.g., as benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and naphthylalkyls having 11 to 13 carbon atoms e.g., α -naphthylmethyl, α -naphthylethyl, β -naphthylmethyl and β -naphthylethyl. Such aromatic hydrocarbon residues include phenyl and naphthyl(α -naphthyl, β -naphthyl).

The above-described heterocyclic ring residue is a 5- or 6-membered ring which contains 1 to 3 atoms other than carbon selected from N, O and S as ring component atoms, and which is bound via carbon. The heterocyclic ring residues include aromatic heterocyclic ring residues such as thienyl (2-thienyl, 3-thienyl), furyl (2-furyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl) and oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), and saturated heterocyclic ring residues such as piperidiny (2-piperidiny, 3-piperidiny, 4-piperidiny), pyrrolidiny (2-pyrrolidiny, 3-pyrrolidiny), morpholinyl (2-morpholinyl, 3-morpholinyl) and tetrahydrofuryl (2-tetrahydrofuryl, 3-tetrahydrofuryl).

The above-described hydrocarbon residue or heterocyclic ring residue may be substituted at any desired position. When the hydrocarbon residue contains an alicyclic residue, or when it is a saturated heterocyclic ring residue, it may have 1 to 3 lower alkyl groups having 1 to 3 carbon atoms (e.g., methyl, ethyl, propyl, or isopropyl) on the ring thereof (including N atoms). When the hydrocarbon residue contains an aromatic hydrocarbon residue, or when it is an aromatic heterocyclic ring residue, it may have 1 to 4 substituents, whether identical or not, on the ring thereof (not including hetero atoms). Examples of these substituents include halogens (fluorine, chlorine and iodine), hydroxy, cyano, trifluoromethyl, lower alkoxy groups (e.g., those having 1 to 4 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy and butoxy), lower alkyl groups (e.g., those having 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl and butyl), lower alkoxy carbonyl groups (e.g., those having 2 to 4 carbon atoms such as methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl) and lower alkylthio groups (e.g., those having 1 to 3 carbon atoms such as methylthio, ethylthio, propylthio and isopropylthio).

When the aromatic 5-membered heterocyclic ring residue represented by A has two or more hydrocarbon residues as substituents thereof, which hydrocarbon residues are located at mutually adjacent positions on the aromatic 5-membered heterocyclic ring, they may bind together to form a condensed ring. This means that the two hydrocarbon residues bind together to form a saturated or unsaturated di-linear hydrocarbon residue having 3 to 5 carbon atoms. Such linear hydrocarbon residues include $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CHCH}_2-$, $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{CH}_2-$ and $-\text{CH}=\text{CH}-\text{CH}_2\text{CH}_2\text{CH}_2-$.

Of the aromatic 5-membered heterocyclic ring residues represented by A, preference is given to the thiazolyl or oxazolyl ring represented by the formula:



wherein R¹ represents hydrogen or an hydrocarbon residue or heterocyclic ring residue which may be substituted; R² represents hydrogen or a lower alkyl (e.g., C₁-C₄, preferably C₁-C₃) group, which may be substituted by an hydroxyl group; R³ and R⁴ independently represent hydrogen or an hydrocarbon residue, which may be substituted, and R³ and R⁴ may be combined together to form a condensed ring; X represents an oxygen atom or a sulfur atom. The hydrocarbon residue and heterocyclic ring residue represented by R¹ and substituents therefor are exemplified by the same hydrocarbon residues, heterocyclic ring residues and substituents therefor as are specified above for the aromatic 5-membered heterocyclic ring residue.

The lower alkyl group represented by R² is exemplified by alkyl groups having 1 to 5 carbon atoms, e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl and pentyl, with a preference being given to those having 1 to 3 carbon atoms. Although these alkyl groups may have an hydroxyl group at any position, the α -position is preferred.

The hydrocarbon residue represented by R³ or R⁴ and substituents therefor are exemplified by the same hydrocarbon residues and substituents therefor as are specified above for the aromatic 5-membered heterocyclic ring residue. R³ and R⁴ may be combined together to form a condensed ring which is the same as the condensed ring formed by an aromatic 5-membered heterocyclic ring residue having two hydrocarbon residues as substituents at mutually adjacent positions.

The thiazolidinedione derivative represented by the general formula (I) is a compound having an acidic nitrogen and a pyridine ring on the thiazolidine ring thereof, involving basic and acidic salts. Examples of basic salts of the thiazolidinedione derivative (I) include metal salts such as the sodium salt, the potassium salt, the aluminium salt, the magnesium salt and the calcium salt. Examples of acidic salts include inorganic acid salts such as the hydrochloride, the sulfate and the hydrobromide, and organic acid salts such as the methanesulfonate and the tartrate.

Compound (I), or a pharmacologically acceptable salt thereof, of the present invention exhibits hypoglycemic action and can be used as such, or in a pharmaceutical composition together with a known pharmacologically acceptable carrier, excipient, filler or diluent, and/or together with one or more known pharmaceutically acceptable additives, in mammals, including humans, as a diabetic remedy. Compound (I), or its pharmacologically acceptable salts, of the present invention also exhibit an improved activity as regards insulin resistance and can also be used as an hypotensor.

Compound (I) of the present invention has a low toxicity. For example, when the compound of Example 1 was orally administered to mice at 15 mg/kg for 4 days, no changes occurred in body weight or liver weight, in comparison with a control. When each of the compounds produced in Examples 2, 5 and 6 was administered orally at 100 mg/kg or intraperitoneally at 50 mg/kg, no deaths occurred.

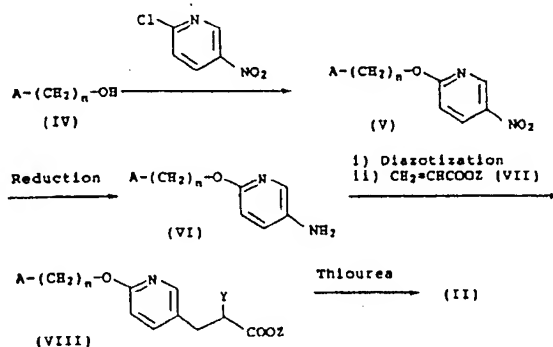
Concerning the method of administration, the compound (I) of the present invention is normally used orally in the form of tablets, capsules (including soft capsules and microcapsules), powders, granules and other forms, but, as the case may be, it can be non-orally administered in the form of injectable preparations, suppositories, pellets and other forms. A single dose is 0.05 to 10 mg/kg for oral administration in adults, preferably 1 to 3 times daily.

A process for the production of the compound (I) of the present invention is now described.

A compound (I-1) can be produced by the hydrolysis of a compound (II). Usually, hydrolysis of the compound (II) is carried out in an appropriate solvent in the presence of water and a mineral acid. Such solvents include alcohols (e.g., methanol, ethanol, propanol, 2-propanol, butanol, isobutanol or 2-methoxyethanol), dimethylsulfoxide, sulfolane and mixtures thereof. Mineral acids include hydrochloric acid, hydrobromic acid and sulfuric acid, the amount used being 0.1 to 20 mols, preferably 0.2 to 10 mols, per mol of compound (II). Water is added in excess relative to the compound (II). This reaction is normally carried out under warming or heating conditions, a normal reaction temperature being 60 to 150°C. Heating time is normally several hours to ten and several hours.

The thiazolidinedione derivative (I) or its salt thus obtained can be isolated and purified by known means of separation and purification such as ordinary concentration, concentration under reduced pressure, crystallization, recrystallization, re-dissolution and chromatography.

The iminothiazolidinone compound (II) used as a starting material for the present method can, for example, be produced as follows:



In the above reaction scheme, Y in formula (VIII) represents an halogen atom such as chlorine, bromine or iodine; Z in formulae (VII) and (VIII) represents an hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl or isobutyl; the other symbols have the same meanings as above.

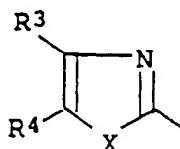
The reaction of compound (IV) to yield compound (V) is effected by condensing compound (IV) and 2-chloro-5-nitropyridine in the presence of, for example, sodium hydride. This reaction can be effected in a solvent such as N,N-dimethylformamide, dioxane, tetrahydrofuran or dimethylsulfoxide at -20 to 60°C. Next, the reaction of compound (V) to yield compound (VI) can easily be carried out by catalytically reducing compound (V) by a conventional method with, for example, palladium-carbon as a catalyst, or by reducing compound (V)

by a conventional method with zinc or iron and acetic acid. Compound (VI) may be isolated as a pure product or may be subjected to the reaction of the next process step without isolation or purification. The reaction of compound (VI) to yield compound (VIII) may be carried out by Meerwein arylation, wherein compound (VI) is diazotized in the presence of hydrogen halide (HY), and then reacted with acrylic acid or an ester thereof (VII) in the presence of a copper catalyst (e.g., cuprous oxide, cupric oxide, cuprous chloride, cupric chloride, cuprous bromide or cupric bromide). Compound (VIII) may be purified by chromatography for example, but may instead be subjected to the reaction of the next process step without intervening isolation or purification.

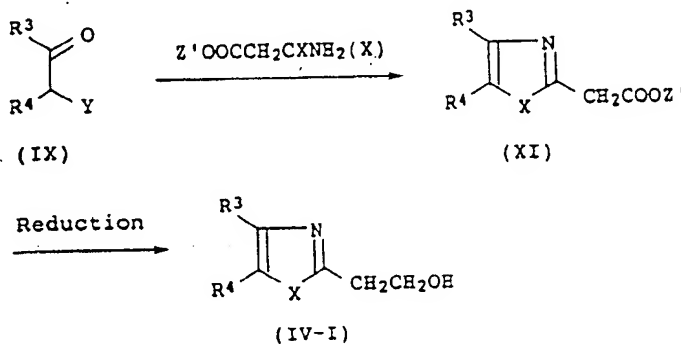
Compound (VIII) may be then reacted with thiourea to yield compound (II). This reaction is carried out normally in a solvent such as an alcohol (e.g., methanol, ethanol, propanol, 2-propanol, butanol, isobutanol or 2-methoxyethanol), dimethylsulfoxide, N,N-dimethylformamide or sulfolane. The reaction temperature is normally 20 to 180°C, preferably 50 to 150°C. The amount of thiourea used is 1 to 2 mols per mol of compound (VIII). As this reaction proceeds, hydrogen halide is formed as a by-product; to trap this by-product, a deacidifying agent such as sodium acetate or potassium acetate may be added. The amount of deacidifying agent used is normally 1 to 1.5 mols per mol of compound (VIII). These reactions eventually produce compound (II), which may be isolated as desired, but the acid hydrolysis process of the present invention may be proceeded to immediately without intervening isolation of the compound (II).

Alcohol (IV) as such is synthesized by, for example, the method described in Japanese Patent Examined Publication No. 85372/1986, or a modification thereof.

Alcohol (IV), which has a group A represented by the following formula:



wherein the various symbols have the same meaning as given above, may, for example, be produced as follows:



wherein Z' represents a lower alkyl group; and the other symbols have the same meanings as are given above.

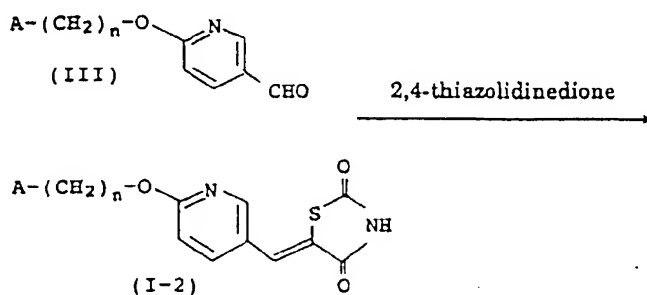
The lower alkyl group represented by Z' is exemplified by alkyl groups having 1 to 4 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl or isobutyl).

In the present method, compound (IX) is reacted with a malonic monoamide or malonic monothioamide derivative (X) to yield compound (XI), which is then reduced to compound (IV-1).

The reaction of (IX) and (X) is carried out in the absence of a solvent or in a solvent which does not affect the reaction. Such solvents include benzene, toluene, xylene, pyridine, chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, dioxane, methanol, ethanol, propanol and isopropanol. The reaction temperature is normally in the range of from 20 to 200°C, preferably 50 to 150°C, the reaction time being in the range of from 30 minutes to 10 hours. The amount of compound (X) used is normally in the range of from 1 to 10 mols, preferably, in the range of from 1 to 5 mols, per mol of compound (IX). This reaction is followed by the reduction of the compound (XI) to the alcohol (IV-1). The reduction reaction may be carried out by one of various known methods, including reduction with metal hydrides, reduction with metal-hydrogen complex compounds, reduction with diborane or substituted borane, or catalytic hydrogenation. In other words, a reduction is achieved by treating

compound (XI) with a reducing agent. Reducing agents include alkali metal borohydrides (e.g., sodium borohydride, lithium borohydride), metal-hydrogen complex compounds such as lithium aluminium hydride, metal hydrides such as sodium hydride, organic tin compounds (e.g., triphenyltin hydride), metals and metal salts such as nickel compounds and zinc compounds, catalytic reducing agents based on a combination with hydrogen of a transition metal such as palladium, platinum or rhodium or diborane. The reduction reaction is carried out in an organic solvent which does not affect the reaction. Such solvents include aromatic hydrocarbons such as benzene, toluene and xylene, halogenated hydrocarbons such as chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, ethers such as diethyl ether, tetrahydrofuran and dioxane, alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol, amides such as N,N-dimethylformamide, and mixtures thereof, chosen as appropriate in terms of the reducing agent employed. The reaction temperature is normally from -20 to 150°C, preferably from 0 to 100°C, the reaction time being from 1 to 24 hours.

Compound (I-2) may be produced by the reaction of compound (III) with 2,4-thiazolidinedione, as follows:



In the above formulae, the various symbols have the same meanings as are given above.

Condensation of compound (III) with 2,4-thiazolidinedione is carried out in a solvent in the presence of a base. The solvent is exemplified by alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol, aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as diethyl ether, di-isopropyl ether, dioxane and tetrahydrofuran, N,N-dimethylformamide, dimethylsulfoxide and acetic acid. The base is exemplified by sodium alkoxides (e.g., sodium methoxide, sodium ethoxide), potassium carbonate, sodium carbonate, sodium hydride, sodium acetate and secondary amines such as piperidine, piperazine, pyrrolidine, morpholine, diethylamine and diisopropylamine. The amount of 2,4-thiazolidinedione used is from 1 to 10 mols, preferably from 1 to 5 mols per mols, of compound (III). The amount of base used is 0.01 to 5 mols, preferably 0.05 to 2 mols, per mol of compound (III). The reaction is normally carried out at from 0 to 150°C, preferably from 20 to 100°C, for from 0.5 to 30 hours.

The 2,4-thiazolidinedione derivative (I-2) thus obtained may be isolated and purified by known means of separation and purification such as ordinary concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, re-dissolution and chromatography.

Compound (I-2) may be converted to compound (I-1) as follows:

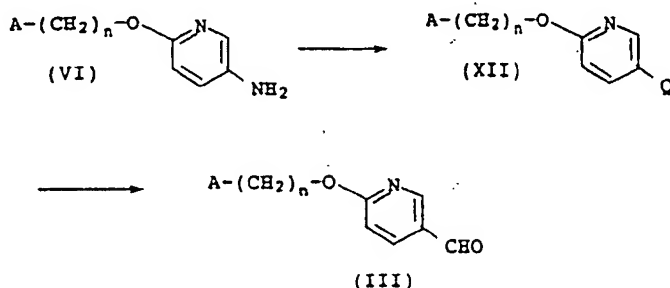


In the above formulae, the various symbols have the same meanings as are given above.

The reduction reaction is carried out in a solvent in the presence of a catalyst in a hydrogen atmosphere of 1 to 150 atm by a conventional method. The solvent is exemplified by alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol, aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as diethyl ether, di-isopropyl ether, dioxane and tetrahydrofuran, halogenated hydrocarbons such as chloroform, dichloromethane and 1,1,2,2-tetrachloroethane, ethyl acetate, acetic acid and mixtures thereof. The reaction is advantageously carried out when a metal catalyst such as a nickel compound catalyst or a transition metal catalyst, e.g. palladium, platinum or rhodium, is used. The reaction temperature is from 0 to 100°C, preferably from 10 to 80°C, the reaction time being from 0.5 to 50 hours.

The 2,4-thiazolidinedione derivative (I-1) thus obtained can be isolated and purified by known means of separation and purification such as ordinary concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, re-dissolution and chromatography.

The pyridine aldehyde derivative (III) used in the present method may, for example, be produced as follows:



In formula (XII), Q represents chlorine, bromine or iodine; the other symbols have the same meaning as are given above.

In this method, compound (VI) is first subjected to the known Sandmeyer reaction to yield the halogen derivative (VII). In this known reaction, the compound (VI) is diazotized via the dropwise addition of an aqueous solution of sodium nitrite (NaNO_2) in a solvent in the presence of hydrochloric acid, hydrobromic acid or hydroiodic acid, followed by reaction with an aqueous solution of sodium halide or potassium halide, to yield the compound (XII). The solvent is exemplified by alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol, ethers such as acetone, 2-butanone, dioxane and tetrahydrofuran and mixtures thereof. The reaction temperature is normally from -50 to 100°C , preferably from -20 to 60°C , the reaction time being 0.5 to 50 hours. Compound (XII) is then treated with butyl lithium, sec-butyl lithium, tert-butyl lithium, methyl-lithium, phenyllithium, phenylmagnesium bromide or the like, after which it is reacted with N, N-dimethylformamide (DMF) to yield compound (III). This reaction is carried out in a solvent by a conventional method. The solvent is exemplified by ethers such as di-ethyl ether, di-isopropyl ether, dioxane and tetrahydrofuran. The amount of N,N-dimethylformamide (DMF) used is 1 to 3 mols, preferably 1 to 2 mols, per mol of compound (XII). The reaction temperature is from -80 to 50°C , preferably from -80 to 20°C , the reaction time being from 0.5 to 50 hours.

The pyridine aldehyde derivative (III) thus obtained may be isolated and purified by known methods of separation and purification such as ordinary concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, re-dissolution and chromatography.

Hypoglycemic and hypolipidemic action in mice

The subject compound, at 0.01% or 0.001% in powdered food (CE-2, Clea Japan), was administered to KKKAY mice (at 10 to 14 weeks of age) for 4 days. The animals had free access to water. Blood was collected from the orbital venous plexus and plasma glucose and plasma triglyceride were assayed by an enzyme method using Iatrochem-GLU(A) and Iatro-MA701TG kit (Iatron). For each item, the percentage reduction from the control group not receiving the test compound was calculated.

Compound (Example No.)	Dose 1) (%)	Hypoglycemic Action (%)	Hypolipidemic 2) Action (%)
1	0.01	56	85
2	0.001	58	51
3	0.001	52	60
4	0.001	31	34
6	0.001	62	71
7	0.001	17	29
8	0.001	17	24
10	0.001	29	14
17	0.001	45	43

1) Concentration of compound in diet

2) Triglyceride lowering action

As stated above, the thiazolidinedione compound (I) of the present invention exhibits an excellent hypoglycemic and hypolipidemic action, and is pharmaceutically useful as a therapeutic agent for diabetes mellitus, hyperlipidemia and hypertension.

The invention is illustrated by the following examples and reference examples.

Example 1

A mixture of 2-imino-5-[[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]methyl]-4-thiazolidinone (0.76 g), 1 N HCl (10 ml) and ethanol (10 ml) was heated for 20 hours while refluxing, followed by concentration under reduced pressure. The residual crystal was collected by filtration, washed with water and then recrystallized from ethanol-chloroform to yield 5-[[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]methyl]-2,4-thiazolidinedione (0.45 g, 59%) as a colorless crystal.

Melting point: 191.0 to 192.0°C

Elemental analysis (for C ₂₁ H ₁₉ N ₃ O ₄ S):			
Calculated:	C, 61.60;	H, 4.68;	N, 10.26
Found :	C, 61.20;	H, 4.66;	N, 10.08

Example 2

5-[[2-[2-(5-methyl-2-(2-thienyl)-4-oxazolyl)ethoxy]-5-pyridyl]methyl]-2,4-thiazolidinedione was obtained in the same manner as in Example 1 (recrystallized from ethanol-chloroform) as a colorless crystal.

Melting point: 174 to 176°C

Example 3

A mixture of 2-bromo-3-[2-[2-(5-methyl-2-phenyl-4-thiazolyl)ethoxy]-5-pyridyl]propionic acid methyl ester (1.40 g), thiourea (0.25 g) and ethanol (20 ml) was heated for 4.5 hours while refluxing, followed by addition of 2 N hydrochloric acid (20 ml) and heating for 18 more hours under refluxing conditions. The reaction mixture was added to water and extracted with dichloromethane. After the dichloromethane layer was washed with water and dried (MgSO₄), the solvent was distilled off. The residual crystal was recrystallized from ethanol-chloroform to yield 5-[[2-[2-(5-methyl-2-phenyl-4-thiazolyl)ethoxy]-5-pyridyl]methyl]-2,4-thiazolidinedione

(0.66 g, 51%) as a colorless crystal.
Melting point: 195.0 to 197.0°C

Example 4

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5-[[[2-[2-[2-(2-furyl)-5-methyl-4-oxazolyl]ethoxy]-5-pyridyl]methyl]-2,4-thiazolidinedione was obtained in the same manner as in Example 3 (recrystallized from ethanol-chloroform) as a colorless crystal.
Melting point: 160.5 ~ 162°C

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Examples 5 - 15

By a similar manner to Example 3, the compounds shown in Table 2 were obtained.

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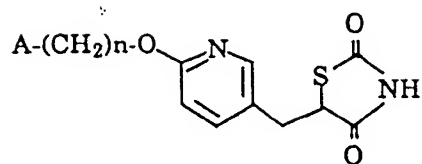
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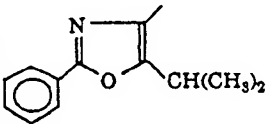
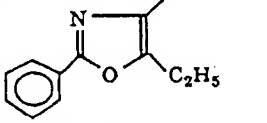
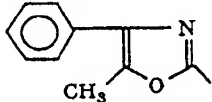
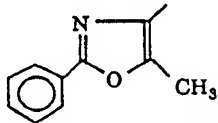
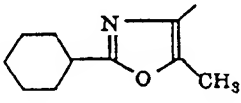
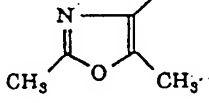
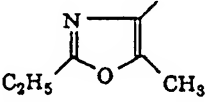
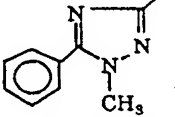
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[Table 2]



Examp le No.	A	n	Yield (%)	Melting point	Recrystallization solvent
5		2	55	141-142	ethyl acetate-ether-hexane
6		2	52	135-136	ethanol-chloroform-ethyl acetate
7		2	4	101-102	ethanol-chloroform-ethyl acetate
8		3	36	134-136	ethyl acetate-hexane-isopropyl ether
9		2	42	113-114	ether-hexane
10		2	11	212-213	ethanol-chloroform-ether
11		2	39	182-183	methanol-dichloromethane-ether
12		2	34	185-186	methanol-chloroform-ether

[Table 2]

Examp le No.	A	n	Yield (%)	Melting point	Recrystallization solvent
13		2	53	127-128	methanol- chloroform-ether
14		2	41	175-176	methanol- chloroform-ether
15		2	59	178-179	methanol- chloroform-ether

Example 16

5-[[2-[2-(4-benzyl-5-methyl-2-oxazolyl)ethoxy]-5-pyridyl]methyl]-2,4-thiazolidinedione, obtained in the same manner as in Example 1, was then recrystallized from ethyl acetate-hexane-isopropyl ether to yield a colorless crystal.

Melting point: 110 - 111°C

Example 17

A mixture of 5-formyl-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (0.6 g), 2,4-thiazolidinedione (0.235 g), piperidine (0.066 ml) and ethanol (20 ml) was heated for 9 hours while refluxing. The reaction mixture was poured into water; the separating crystal, collected by filtration, was then recrystallized from ethanol-chloroform to yield 5-[[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]methylidene]-2,4-thiazolidinedione (0.232 g, 29%) as a yellow crystal.

Melting point: 195 - 196°C

Example 18

A mixture of 2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-pyridinecarboxyaldehyde (1.20g), 2,4-thiazolidinedione (720mg), piperidine (175mg) and ethanol (30ml) were heated under reflux for 10 hours. Water was added to the reaction mixture, and the separating crystals were collected by filtration and washed with ethanol to obtain 5-[[2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-pyridyl]methylidene]-2,4-thiazolidinedione (1.35g, 85%). Recrystallization from dichloromethane-methanol gave colorless needles.

Melting point: 225-226°C.

Elemental analysis (for C ₂₀ H ₁₅ N ₃ O ₄ S)			
Calculated:	C, 61.06;	H, 3.84;	N, 10.68
Found :	C, 60.82;	H, 3.72;	N, 10.76

Example 19

A mixture of 5-[[2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-pyridyl]methylidene]-2,4-thiazolidinedione (1.00g), palladium-carbon (5%, 1.00g) and tetrahydrofuran (80ml) was subjected to catalytic reduction at room temperature and 1 atm for 6 hours. The catalyst was filtered off, and palladium-carbon (2.00g) was added

and the mixture was further subjected to catalytic reduction at room temperature and 1 atm for 6 hours. The catalyst was filtered off. The filtrate was evaporated under reduced pressure and the residue was subjected to silica gel column chromatography. From the fraction eluted with 2% methanol-chloroform, crystals (520mg, 52%) of 5-[[2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-pyridyl]methyl]-2,4-thiazolidinedione were obtained. Recrystallization from dichloromethane-isopropyl ether gave colorless prisms. Melting point: 151-152°C

Elemental analysis (for C ₂₆ H ₁₇ N ₃ O ₄)			
Calculated:	C, 60.75;	H, 4.33;	N, 10.63
Found :	C, 60.52;	H, 4.36;	N, 10.48

Example 20

By a similar manner to Example 3, 5-[[2-[2-[2-(2-chlorophenyl)-5-methyl-4-oxazolyl]ethoxy]-5-pyridyl]methyl]-2,4-thiazolidinedione was obtained. Recrystallization from methanol-dichloroethane-diethyl ether gave colorless crystals. Melting point: 176-177°C

Reference Example 1

To a solution of 2-chloro-5-nitropyridine (25 g) and 2-(5-methyl-2-phenyl-4-oxazolyl)ethanol (32.1 g) in THF (250 ml), sodium hydride in oil (60%, 6.92 g) was added gradually while the solution was stirred under ice cooling conditions. The reaction mixture was stirred at room temperature for 15 more hours, after which it was added to water and extracted with ethyl acetate. After the ethyl acetate layer was washed with water and dried (MgSO₄), the solvent was distilled off under reduced pressure. The residual crystal was collected by filtration and recrystallized from ethanol to yield 2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-nitropyridine (25.4 g, 49%) as a yellow-brown crystal. Melting point: 110.5 to 111.5°C

Elemental analysis (for C ₁₇ H ₁₅ N ₃ O ₄):			
Calculated:	C, 62.76;	H, 4.65;	N, 12.92
Found :	C, 62.80;	H, 4.58;	N, 12.96

Reference Example 2

2-[2-(5-methyl-2-(2-thienyl)-4-oxazolyl)ethoxy]-5-nitropyridine was obtained in the same manner as in Reference Example 1 (recrystallized from ethyl acetate-hexane) as a light yellow crystal. Melting point: 125.5 to 126°C

Reference Example 3

2-[2-(2-(2-furyl)-5-methyl-4-oxazolyl)ethoxy]-5-nitropyridine was obtained in the same manner as in Reference Example 1 (recrystallized from ethyl acetate-hexane) as a light yellow crystal. Melting point: 120.0 to 121.5°C

Reference Example 4

2-[2-(5-methyl-2-phenyl-4-thiazolyl)ethoxy]-5-nitropyridine was obtained in the same manner as in Reference Example 1 (recrystallized from ethyl acetate-hexane) as a light yellow crystal. Melting point: 131.0 to 132.0°C

Reference Example 5

A mixture of 2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-nitropyridine (13.4 g), palladium-carbon (5%, 1.5 g), ethyl acetate (200 ml), and methanol (150 ml) was catalytically reduced at room temperature at 1 atm.

After the catalyst was filtered off, the filtrate was concentrated under reduced pressure, and the resulting residual crystal was collected by filtration and recrystallized from ethyl acetate-hexane to yield 5-amino-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (11.4 g, 93%) as a brown crystal.

Melting point: 107.0 to 108.0°C

Elemental analysis (for C ₁₇ H ₁₇ N ₃ O ₂):			
Calculated:	C, 69.14;	H, 5.80;	N, 14.23
Found :	C, 69.01;	H, 5.94;	N, 13.99

Reference Example 6

5-amino-2-[2-(5-methyl-2-(2-thienyl)-4-oxazolyl)ethoxy]pyridine was obtained in the same manner as in Reference Example 5 (recrystallized from ethyl acetate-hexane) as a light brown crystal.

Melting point: 120 to 122°C

Reference Example 7

5-amino-2-[2-[2-(2-furyl)-5-methyl-4-oxazolyl)ethoxy]pyridine was obtained in the same manner as in Reference Example 5 (recrystallized from ethyl acetate-ether-hexane) as a light brown crystal.

Melting point: 88.0 to 90.0°C

Reference Example 8

5-amino-2-[2-(5-methyl-2-phenyl-4-thiazolyl)ethoxy]pyridine was obtained in the same manner as in Reference Example 5 (recrystallized from ethyl acetate-ether-hexane) as a light brown crystal.

Melting point: 89.0 to 91.0°C

Reference Example 9

To a mixture of 5-amino-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (4.5 g), aqueous HBr (47%, 7.1 ml) and acetone (70 ml) was added an aqueous solution of sodium nitrite (NaNO₂) (1.17 g) in water (5 ml) dropwise at a temperature of under 10°C. After stirring at 10°C for 30 minutes, the temperature was increased to 30°C, and methyl acrylate (8.3 ml) was added. Then, cuprous oxide (Cu₂O) (0.1 g) was added little by little, and the mixture was vigorously stirred. The reaction mixture was further stirred at 40 to 45°C for 1 more hour and then concentrated under reduced pressure. After alkalization with concentrated aqueous ammonia, the residue was extracted with ethyl acetate. After the ethyl acetate layer was washed with water and dried (MgSO₄), the solvent was distilled off under reduced pressure. The residual oily substance was subjected to silica gel chromatography. From the fraction eluted with ethyl acetate-hexane (2:1, v/v), 2-bromo-3-[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]propionic acid methyl ester (4.7 g, 68%) was obtained. NMR (δ ppm in CDCl₃): 2.34 (3H, s), 2.98 (2H, t, \underline{J} = 6.7 Hz), 3.16 (1H, dd, \underline{J} = 7.0 & 14.5 Hz), 3.37 (1H, dd, \underline{J} = 8.0 & 14.5 Hz), 3.74 (3H, s), 4.31 (1H, dd, \underline{J} = 8.0 & 7.0 Hz), 4.55 (2H, t, \underline{J} = 6.7 Hz), 6.67 (1H, d, \underline{J} = 8.6 Hz), 7.35-7.50 (4H, m), 7.90-8.05 (3H, m)

Reference Example 10

2-bromo-3-[2-[2-[5-methyl-2-(2-thienyl)-4-oxazolyl]ethoxy]-5-pyridyl]propionic acid methyl ester was obtained in the same manner as in Reference Example 9. NMR (δ ppm in CDCl₃): 2.31 (3H, s), 2.95 (2H, t, \underline{J} = 6.7 Hz), 3.16 (1H, dd, \underline{J} = 7.2 & 14.4 Hz), 3.37 (1H, dd, \underline{J} = 8.2 & 14.4 Hz), 3.74 (3H, s), 4.32 (1H, dd, \underline{J} = 8.0 & 7.2 Hz), 4.52 (2H, t, \underline{J} = 6.8 Hz), 6.66 (1H, d, \underline{J} = 8.4 Hz), 7.07 (1H, dd, \underline{J} = 5.0 & 3.6 Hz), 7.36 (1H, dd, \underline{J} = 5.0 & 1.2 Hz), 7.42 (1H, dd, \underline{J} = 8.4 & 2.6 Hz), 7.58 (1H, dd, \underline{J} = 3.7 & 1.1 Hz), 7.99 (1H, d, \underline{J} = 2.2 Hz)

Reference Example 11

2-bromo-3-[2-[2-[2-(2-furyl)-5-methyl-4-oxazolyl]ethoxy]-5-pyridyl]propionic acid methyl ester was obtained in the same manner as in Reference Example 9. NMR (δ ppm in CDCl₃): 2.32 (3H, s), 2.96 (2H, t, \underline{J} =

6.7 Hz), 3.16 (1H, dd, $J = 7.4$ & 14.4 Hz), 3.37 (1H, dd, $J = 8.1$ & 14.6 Hz), 3.74 (3H, s), 4.32 (1H, dd, $J = 8.2$ & 7.2 Hz), 4.54 (2H, t, $J = 6.7$ Hz), 6.51 (1H, dd, $J = 3.4$ & 1.8 Hz), 6.66 (1H, d, $J = 8.4$ Hz), 6.92 (1H, d, $J = 3.6$ Hz), 7.43 (1H, dd, $J = 8.5$ & 2.5 Hz), 7.52 (1H, d, $J = 1.8$ Hz), 8.00 (1H, d, $J = 2.6$ Hz)

5 Reference Example 12

2-bromo-3-[2-[2-(5-methyl-2-phenyl-4-thiazolyl)ethoxy]-5-pyridyl]propionic acid methyl ester was obtained in the same manner as in Reference Example 9. NMR (δ ppm in CDCl_3): 2.43 (3H, s), 3.16 (1H, dd, $J = 7.1$ & 14.5 Hz), 3.19 (2H, t, $J = 7.0$ Hz), 3.37 (1H, dd, $J = 8.1$ & 14.3 Hz), 3.74 (3H, s), 4.32 (1H, dd, $J = 8.1$ & 7.2 Hz), 4.63 (2H, t, $J = 7.0$ Hz), 6.67 (1H, d, $J = 8.4$ Hz), 7.34-7.47 (4H, m), 7.83-7.93 (2H, m), 8.01 (1H, d, $J = 2.6$ Hz)

Reference Example 13

15 A mixture of 2-bromo-3-[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]propionic acid methyl ester (1.07 g), thiourea (0.2 g), sodium acetate (0.22 g) and ethanol (25 ml) was heated for 2.5 hours while refluxing. To the reaction mixture was added a saturated aqueous solution of NaHCO_3 and ether, and the resulting crystal was collected by filtration, to yield 2-imino-5-[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]-4-thiazolidinone (0.86 g, 88%) (recrystallized from chloroform-methanol) as a colorless crystal.

20 Melting point: 213 to 214°C

Elemental analysis (for $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$):			
Calculated:	C, 61.75;	H, 4.94;	N, 13.72
Found :	C, 61.76;	H, 5.00;	N, 13.89

Reference Example 14

30 2-Imino-5-[2-[2-[5-methyl-2-(2-thienyl)-4-oxazolyl]ethoxy]-5-pyridyl]-4-thiazolidinone was obtained in the same manner as in Reference Example 13 (recrystallized from ethanol-chloroform) as a colorless crystal. Melting point: 193 to 194.5°C

35 Reference Example 15

By a similar manner to Reference Example 13, 5-[2-[2-(4-benzyl-5-methyl-2-oxazolyl)ethoxy]-5-pyridyl]methyl]-2-imino-4-thiazolidinone was obtained. Recrystallization from methanol-chloroform-ether gave colorless crystals. Melting point 135-136°C.

40 Reference Examples 16 - 27

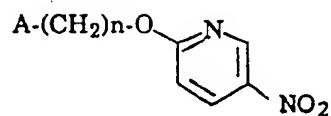
By a similar manner to Reference Example 1, compounds shown in Tables 3 and 4 were obtained.

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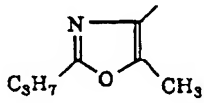
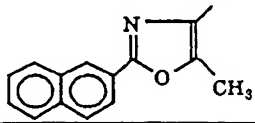
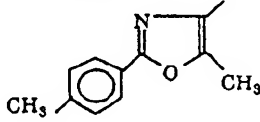
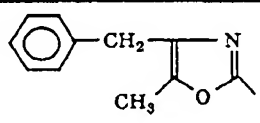
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[Table 3]



Reference Example No	A	n	Yield (%)	Melting point	Recrystallization solvent
16		2	53	91-92	ethyl acetate- hexane
17		2	64	100-101	ethyl acetate hexane
18		2	70	119-120	ethyl acetate- hexane
19		3	58	103-104	ethyl acetate- hexane-isopropyl ether
20		2	86	70-71	ethyl acetate hexane
21		2	82	83-84	ether-hexane
22		2	55	85-86	ether-hexane
23		2	71	152-153	ethyl acetate- ether

[Table 4]

Reference Example No	A	n	Yield (%)	Melting point	Recrystallization solvent
24		2	65	63-64	ether-hexane
25		2	59	122-123	ethyl acetate-isopropyl ether
26		2	80	127-128	ethyl acetate-hexane
27		2	83	oil 1)	

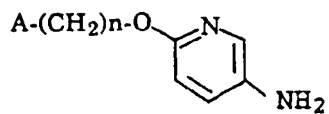
1) Purified by column chromatography on silica gel.

NMR (δ ppm) in CDCl_3 : 2.20(3H,s), 3.20(2H,t, $J=6.7\text{Hz}$), 3.77(2H,s), 4.79(2H,t, $J=6.8\text{Hz}$), 6.80(1H,d, $J=9.2\text{Hz}$), 7.10-7.37(5H,m), 8.33(1H,dd, $J=2.8$ & 9.2Hz), 9.04(1H,d, $J=3.0\text{Hz}$).

Reference Examples 28 - 39

By a similar manner to Reference Example 5, compounds shown in Tables 5 and 6 were obtained.

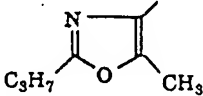
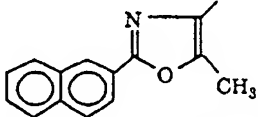
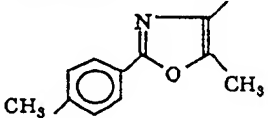
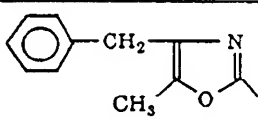
[Table 5]



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Reference Example No	A	n	Yield (%)	Melting point	Recrystallization solvent
15 28		2	93	125-126	ethyl acetate- isopropyl ether- hexane
20 29		2	91	114-115	ethyl acetate- isopropyl ether hexane
25 30		2	quant.	oil 1)	
30 31		3	92	oil 2)	
32		2	95	oil 3)	
35 33		2	99	oil 4)	
40 34		2	quant.	oil 5)	
45 35		2	98	160-161	methanol- isopropyl ether

[Table 6]

Reference Example No	A	n	Yield (%)	Melting point	Recrystallization solvent
36		2	99	oil 6)	
37		2	85	131-132	ethyl acetate-isopropyl ether
38		2	89	137-138	ethyl acetate-hexane-isopropyl ether
39		2	98	oil 7)	

1) NMR (δ ppm in CDCl_3) : 2.50(3H,s), 3.23(2H,t, \underline{J} = 6.8Hz), 4.62(2H,t, \underline{J} = 6.9Hz), 6.60(1H,d, \underline{J} = 8.8Hz), 7.02(1H,dd, \underline{J} = 2.8&8.6Hz), 7.22-7.46(3H,m), 7.58-7.68(3H,m).

2) NMR (δ ppm in CDCl_3) : 2.03-2.23(2H,m), 2.82(3H,s), 2.67(2H,t, \underline{J} = 7.4Hz), 4.21(2H,t, \underline{J} = 6.3Hz), 6.60(1H,d, \underline{J} = 8.8Hz), 7.03(1H,dd, \underline{J} = 3.0&8.6Hz), 7.37-7.49(3H,m), 7.64(1H,d, \underline{J} = 3.0Hz), 7.92-8.03(2H,m).

3) NMR (δ ppm in CDCl_3) : 1.17-1.93(8H,m), 1.93-2.13(2H,m), 2.20(3H,s), 2.59-2.77(1H,m), 2.85(2H,t, \underline{J} = 6.9Hz), 4.38(2H,t, \underline{J} = 6.9Hz), 6.57(1H,d, \underline{J} = 8.6Hz), 7.03(1H,dd, \underline{J} = 3.0&8.6Hz), 7.64(1H,d, \underline{J} = 3.0Hz).

4) NMR (δ ppm in CDCl_3) : 2.20(3H,s), 2.37(3H,s), 2.83(2H,t, \underline{J} = 6.8Hz), 4.39(2H,t, \underline{J} = 6.8Hz), 6.56(1H,d, \underline{J} = 8.8Hz), 7.02(1H,dd, \underline{J} = 2.8&8.8Hz), 7.64(1H,d, \underline{J} = 2.8Hz).

5) NMR (δ ppm in CDCl_3) : 1.29(3H,t, \underline{J} = 7.6Hz), 2.20(3H,s), 2.69(2H,q, \underline{J} = 7.6Hz), 2.84(2H,t, \underline{J} = 6.9Hz), 4.39(2H,t, \underline{J} = 6.9Hz), 6.55(1H,d, \underline{J} = 8.6Hz), 7.01(1H,dd, \underline{J} = 3.0&8.6Hz), 7.63(1H,d, \underline{J} = 3.0Hz).

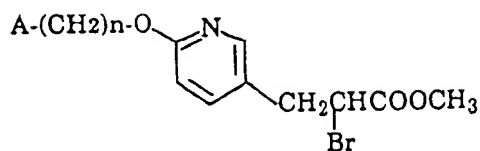
6) NMR (δ ppm in CDCl_3) : 0.97(3H,t, \underline{J} = 7.3Hz), 1.64-1.85(2H,m), 2.20(3H,s), 2.64(2H,t, \underline{J} = 7.5Hz), 2.84(2H,t, \underline{J} = 7.0Hz), 4.39(2H,t, \underline{J} = 6.9Hz), 6.56(1H,d, \underline{J} = 8.8Hz), 7.02(1H,dd, \underline{J} = 3.0&8.8Hz), 7.64(1H,d, \underline{J} = 3.0Hz).

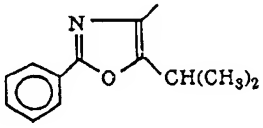
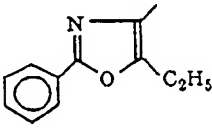
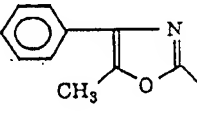
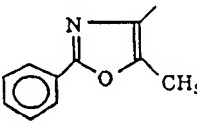
7) NMR (δ ppm in CDCl_3) : 2.18(3H,s), 3.14(2H,t, $J=6.9\text{Hz}$), 3.77(2H,s),
4.55(2H,t, $J=6.9\text{Hz}$), 6.57(1H,d, $J=8.4\text{Hz}$), 7.00(1H,dd, $J=3.0\&8.6\text{Hz}$), 7.14-
7.33(5H,m), 7.62(1H,d, $J=3.0\text{Hz}$).

Reference Examples 40-51

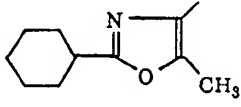
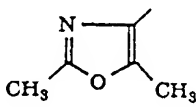
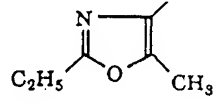
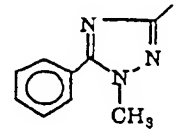
By a similar manner to Reference Example 9, compounds shown in Tables 7, 8 and 9 were obtained in oily substance.

[Table 7]

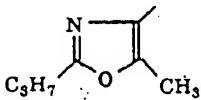
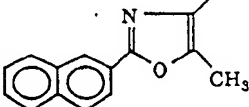
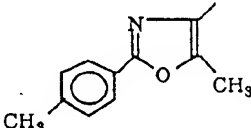
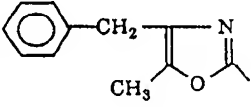


Reference Example No.	A	n	Yield (%)	NMR (δ ppm in CDCl_3)
40		2	53	1.32(6H,d, $J=7\text{Hz}$), 2.96-3.21 (4H, m), 3.37(1H,dd, $J=8.1$ & 14.3Hz), 4.31(1H,dd, $J=8.1$ & 7.0Hz), 4.55(2H,t, $J=6.7\text{Hz}$), 6.66(1H,d, $J=8.4\text{Hz}$), 7.37-7.49(4H,m), 7.95-8.40 (3H,m).
41		2	56	1.27(3H,t, $J=7.5\text{Hz}$), 2.70(2H, q, $J=7.5\text{Hz}$), 2.98(2H,t, $J=6.8$ Hz), 3.16(1H,dd, $J=7.2$ & 14.4 Hz), 3.37(1H,dd, $J=8.2$ & 14.4 Hz), 3.74(3H,s), 4.31(1H,dd, $J=8.2$ & 7.2Hz), 4.54(2H,t, $J=6.7\text{Hz}$), 6.66(1H,d, $J=8.6\text{Hz}$), 7.36-7.48 (4H,m), 7.92-8.02 (3H,m).
42		2	53	2.50(3H,s), 3.10-3.45(4H,m), 3.75(3H,s), 4.32(1H,dd, $J=8.0$ & 7.2Hz), 4.70(2H,t, $J=6.8\text{Hz}$), 6.70(1H,d, $J=8.4$ Hz), 7.23-7.48(4H,m), 7.59-7.68(2H,m), 8.00(1H,d, $J=2.6$ Hz)
43		3	36	2.05-2.25(2H,m), 2.29(3H,s), 2.67(2H,q, $J=7.3\text{Hz}$), 3.16(1H, dd, $J=7.2$ & 14.4Hz), 3.38(1H,d, $J=8.0$ & 14.4Hz), 3.75(3H,s), 4.24-4.38 (3H,m), 6.70(1H,d, $J=8.4\text{Hz}$), 7.36-7.49(4H,m), 7.92-8.04(3H,m).

[Table 8]

Reference Example No.	A	n	Yield (%)	NMR (δ ppm in CDCl_3)
44		2	44	1.21-2.18(10H,m), 2.21(3H,s), 2.60-2.78(1H,m), 2.87(2H,t, $J=6.9\text{Hz}$), 3.16(1H,dd, $J=7.2\&14.4\text{Hz}$), 3.37(1H,dd, $J=8.1\&4.3\text{Hz}$), 3.74(3H,s), 4.32(1H,dd, $J=8.0\&7.2\text{Hz}$), 4.45(2H,t, $J=6.9\text{Hz}$), 6.66(1H,d, $J=8.4\text{Hz}$), 7.42(1H,dd, $J=2.5\&8.5\text{Hz}$), 7.98(1H,dd, $J=2.4\text{Hz}$).
45		2	34	2.20(3H,s), 2.37(3H,s), 2.85(2H,t, $J=6.8\text{Hz}$), 3.16(1H,dd, $J=7.1\&14.3\text{Hz}$), 3.37(1H,dd, $J=8.0\&14.4\text{Hz}$), 3.75(3H,s), 4.32(1H,dd, $J=7.2\&8.2\text{Hz}$), 4.47(2H,t, $J=6.8\text{Hz}$), 6.65(1H,d, $J=8.6\text{Hz}$), 7.42(1H,dd, $J=2.6\&8.4\text{Hz}$), 7.99(1H,d, $J=2.4\text{Hz}$).
46		2	51	1.29(3H,t, $J=7.7\text{Hz}$), 2.21(3H,s), 2.70(2H,q, $J=7.6\text{Hz}$), 2.87(2H,t, $J=6.9\text{Hz}$), 3.16(1H,dd, $J=7.1\&14.3\text{Hz}$), 3.37(1H,dd, $J=8.1\&14.3\text{Hz}$), 3.75(3H,s), 4.32(1H,dd, $J=7.2\&8.1\text{Hz}$), 4.46(2H,t, $J=6.8\text{Hz}$), 6.66(1H,d, $J=8.4\text{Hz}$), 7.42(1H,dd, $J=2.5\&8.5\text{Hz}$), 7.99(1H,d, $J=2.6\text{Hz}$).
47		2	45	3.10-3.46(4H,m), 3.74(3H,s), 3.92(3H,s), 4.32(1H,t, $J=7.5\text{Hz}$), 4.70(2H,t, $J=6.6\text{Hz}$), 6.67(1H,d, $J=8.4\text{Hz}$), 7.30-7.50(4H,m), 7.97-8.12(3H,m).

[Table 9]

Reference Example No.	A	n	Yield (%)	NMR (δ ppm in CDCl ₃)
48		2	32	0.97(3H,t, J =7.3Hz),1.64-1.85(2H,m),2.21(3H,s),2.64(2H,t, J =7.5Hz),2.87(2H,t, J =6.9Hz),3.16(1H,dd, J =7.2&14.4Hz),3.37(1H,dd, J =8.1&14.5Hz),3.75(3H,s),4.32(1H,dd, J =7.2&8.2Hz),4.46(2H,t, J =6.8Hz),6.66(1H,d, J =8.4Hz),7.42(1H,dd, J =2.6&8.4Hz),7.99(1H,d, J =2.6Hz).
49		2	28	2.38(3H,s),3.02(2H,t, J =6.0Hz),3.16(1H,dd, J =7.2&14.4Hz),3.37(1H,dd, J =8.0&14.2Hz),3.74(3H,s),4.32(1H,dd, J =7.1&8.1Hz),4.58(2H,t, J =6.8Hz),6.68(1H,d, J =8.4Hz),7.38-7.57(3H,m),7.79-7.96(3H,m),8.08(1H,dd, J =1.7&8.7Hz),8.10(1H,d, J =2.6Hz),8.47(1H,s)
50		2	36	2.32(3H,s),2.38(3H,s),2.97(2H,t, J =6.8Hz),3.16(1H,dd, J =7.2&14.4Hz),3.37(1H,dd, J =8.0&14.4Hz),3.74(3H,s),4.32(1H,dd, J =7.3&8.2Hz),4.54(2H,t, J =6.8Hz),6.67(1H,d, J =8.4Hz),7.23(1H,d, J =8.0Hz),7.43(1H,dd, J =2.6&8.4Hz),7.87(2H,d, J =8.2Hz),8.00(1H,d, J =2.6Hz).
51		2	45	2.18(3H,s),3.08-3.23(3H,m),3.37(1H,dd, J =8.1&14.5Hz),3.75(3H,s),3.77(2H,s),4.32(1H,dd, J =8.0&7.2Hz),4.63(2H,t, J =6.9Hz),6.67(1H,d, J =8.4Hz),7.13-7.34(5H,m),7.42(1H,dd, J =2.5&8.5Hz),7.98(1H,d, J =2.2Hz)

Reference Example 52

To a mixture of 5-amino-2-[2-(5-methyl-2-phenyl-4-oxazolyl) ethoxy]pyridine (10.0 g), conc. HCl (8.47 ml) and acetone (100 ml), a solution of sodium nitrite (NaNO_2) (2.46 g) in water (10 ml) was added dropwise at a temperature of under 10°C . After mixture was stirred at 10°C for 30 minutes, a solution of potassium iodide (KI) (2.46 g) in water (10 ml) was added dropwise to the mixture. The reaction mixture was stirred at 30 to 35°C for 1 hour and then at 35 to 40°C for 1 hour, after which it was concentrated under reduced pressure. The residue was poured into water and extracted with ethyl acetate. After the ethyl acetate layer was washed with water and dried (MgSO_4), the solvent was distilled off under reduced pressure. The residual oily substance was subjected to silica gel chromatography. From the fraction eluted with ethyl acetate-hexane (1:3, v/v), 5-iodo-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (7.22 g, 52%) was obtained, which was then recrystallized from ethyl acetate-hexane to yield a colorless crystal. Melting point: $105 - 106^\circ\text{C}$

Reference Example 53

To a solution of 5-iodo-2-[2-(5-methyl-2-phenyl-4-oxazolyl) ethoxy]pyridine (2.5 g) in tetrahydrofuran (40 ml), a solution of n-butyl lithium in hexane (1.6 M, 4.61 ml) was added dropwise at -65°C in a nitrogen stream. After the mixture was stirred at the same temperature for 15 minutes, N,N-dimethylformamide (0.71 ml) was added dropwise. After the cooling bath was removed and the mixture was stirred for 30 more minutes, a saturated aqueous solution of ammonium chloride (6 ml) was added. The reaction mixture was poured into water and extracted with ethyl acetate. After the ethyl acetate layer was washed with water and dried (MgSO_4), the solvent was distilled off under reduced pressure, to yield 5-formyl-2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]pyridine (1.5 g, 79%), which was then recrystallized from ethyl acetate-hexane to yield a colorless crystal. Melting point: $99 - 100^\circ\text{C}$

Reference Example 54

A mixture of N-carbobenzoxyphenylalanine (40 g), acetic anhydride (54.7 g) and 4-(N,N-dimethylamino)pyridine (DMAP) (1.0 g) was stirred at 80°C for 2 hours. The reaction mixture was poured into water, stirred for 2 hours and then extracted with ethyl acetate. After the ethyl acetate layer was washed successively with 2N HCl, water, a saturated aqueous solution of sodium hydrogen carbonate and water and then dried (MgSO_4), the solvent was distilled off under reduced pressure, to yield 3-acetylamino-4-phenyl-2-butanone (13.5 g, 49%), which was then recrystallized from ethyl acetate-isopropyl ether to yield a colorless crystal. Melting point: $96 - 97^\circ\text{C}$

Reference Example 55

A mixture of 3-acetylamino-4-phenyl-2-butanone (12.5 g), 6N HCl (50 ml) and ethanol (50 ml) was stirred under refluxing conditions for 18 hours. The reaction mixture was concentrated under reduced pressure to yield 3-amino-4-phenyl-2-butanone hydrochloride (9.8 g, 81%).

Reference Example 56

A mixture of 3-amino-4-phenyl-2-butanone hydrochloride (9.56 g), ethyl malonyl chloride (7.72 g) and benzene (40 ml) was stirred under refluxing conditions for 4 hours. The reaction mixture was concentrated under reduced pressure; the residue was then neutralized with a saturated aqueous solution of sodium carbonate and extracted with ethyl acetate. After the ethyl acetate layer was washed with water and dried (MgSO_4), the solvent was distilled off under reduced pressure, to yield N-(1-benzyl-2-oxopropyl)malonamidic acid ethyl ester (7.45 g, 56%), which was then recrystallized from ethyl acetate-isopropyl ether to yield a colorless crystal. Melting point: $68 - 69^\circ\text{C}$

Reference Example 57

A mixture of N-(1-benzyl-2-oxopropyl)malonamidic acid ethyl ester (7.0 g), phosphorus oxychloride (POCl_3) (5.8 g) and toluene (40 ml) was stirred under refluxing conditions for 1 hour. The reaction mixture was concentrated under reduced pressure; the residue was then neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. After the ethyl acetate layer was washed with

water and dried (MgSO_4), the solvent was distilled off under reduced pressure and the residue was subjected to silica gel chromatography. From the fraction eluted with hexane-ethyl acetate (1:3, v/v), ethyl 2-(4-benzyl-5-methyl-2-oxazolyl)acetate (4.76 g, 63%) was obtained as an oily substance.

NMR (δ ppm in CDCl_3): 1.26 (3H, t, $J = 7.1$ Hz), 2.21 (3H, s), 3.75 (2H, s), 3.79 (2H, s), 4.19 (2H, q, $J = 7.1$ Hz), 7.13-7.34 (5H, m)

Reference Example 58

To a suspension of lithium aluminum hydride (LiAlH_4) (0.7 g) in ethyl ether (40 ml), a solution of ethyl 2-(4-benzyl-5-methyl-2-oxazolyl)acetate (4.76 g) in ethyl ether (60 ml) was added dropwise under ice cooling conditions, followed by stirring for 1 hour. After water (5 ml) was added dropwise to the reaction mixture, the insoluble substances were filtered off, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel chromatography. From the fraction eluted with chloroform-ethyl acetate (2:1, v/v), 2-(4-benzyl-5-methyl-2-oxazolyl)ethanol (3.0 g, 75%) was obtained as an oily substance.

NMR (δ ppm in CDCl_3): 3.19 (3H, s), 2.88 (2H, t, $J = 5.7$ Hz), 3.75 (2H, s), 3.94 (2H, t, $J = 5.8$ Hz), 7.13-7.36 (5H, m)

Reference Example 59

Methylhydrazine (3.5 g) was added gradually to an ice-cooled solution of methyl benzimidate hydrochloride [$\text{C}_6\text{H}_5\text{C}(\text{=NH})\text{OCH}_3\cdot\text{HCl}$] (13.0 g) in methanol (80 ml), followed by stirring at the same temperature for 3 hours. The separating crystal was collected by filtration to yield 2-methyl-3-phenylamidorazone hydrochloride (10.9 g), which was then recrystallized from methanol-ether.

Melting point: 197 - 198°C

Reference Example 60

A mixture of 2-methyl-3-phenylamidorazone hydrochloride (6.0 g), ethyl malonyl chloride (5.1 g) and benzene (40 ml) was stirred under refluxing conditions for 6 hours. The reaction mixture was concentrated under reduced pressure, and acetic acid (30 ml) added to the residue, followed by stirring under refluxing conditions for 3 hours. The reaction mixture was concentrated under reduced pressure; the residue was then neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. After the ethyl acetate layer was washed with water and dried (MgSO_4), the solvent was distilled off under reduced pressure and the residue was subjected to silica gel chromatography. From the fraction eluted with chloroform-ethyl acetate (4:1, v/v), 1-methyl-5-phenyl-1H-1,2,4-triazol-3-ylacetic acid ethyl ester (6.2 g, 78%) was obtained, which was then recrystallized from ether-isopropyl ether to yield colorless prisms.

Melting point: 82 - 83°C

Reference Example 61

To a mixture of aspartic acid β -methyl ester (20.0 g), sodium hydrogen carbonate (24.0 g), ethyl ether (50 ml) and water (200 ml), 2-naphthoyl chloride (25.9 g) was added dropwise under ice cooling conditions. After the mixture was stirred at room temperature for 3 hours, the organic layer was separated. The water layer was acidified with 2N HCl and then extracted with ethyl acetate. After the ethyl acetate layer was washed with water and dried (MgSO_4), the solvent was distilled off under reduced pressure to yield an oily substance.

The oily substance was added to a mixture of acetic anhydride (69.5 g), 4-(N,N-dimethylamino)pyridine (DMAP) (0.5 g) and pyridine (64 ml), followed by stirring at 90°C for 1 hour. The reaction mixture was poured into water and stirred for 2 hours, after which it was extracted with ethyl acetate. After the ethyl acetate layer was washed successively with a saturated aqueous solution of sodium hydrogen carbonate, a dilute aqueous solution of phosphoric acid and water, and then dried (MgSO_4), the solvent was distilled off under reduced pressure to yield an oily substance.

The oily substance was dissolved in acetic anhydride (40 ml), and concentrate H_2SO_4 (4.0 ml) was added dropwise at room temperature. This mixture was stirred at 90°C for 1 hour and then concentrated under reduced pressure. The residue was poured into water, neutralized with a saturated aqueous solution of sodium hydrogen carbonate and then extracted with ethyl acetate. After the ethyl acetate layer was washed with water and dried (MgSO_4), the solvent was distilled off under reduced pressure to yield 5-methyl-2-(2-naphthyl)-4-oxazoleacetic acid methyl ester (31 g, 81%), which was then recrystallized from dichloromethane-isopropyl ether to yield colorless prisms.

Melting point: 86 - 87°C

Reference Example 62

5-methyl-2-(4-methylphenyl)-4-oxazoleacetic acid methyl ester, obtained in the same manner as in Reference Example 61, was then recrystallized from ethyl acetate-hexane to yield a colorless crystal.
Melting point: 59 - 60°C

Reference Example 63

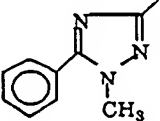
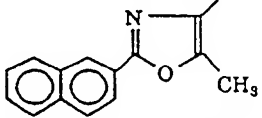
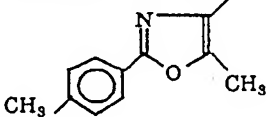
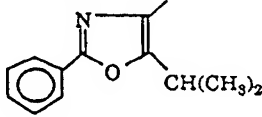
5-Isopropyl-2-phenyl-4-oxazoleacetic acid methyl ester was obtained in the same manner as in Reference Example 61.
NMR (δ ppm in CDCl_3): 1.33 (6H, d, $J=7$ Hz), 3.0-3.2(1H,m), 3.61 (2H, s), 3.73 (3H, s), 7.35-7.50 (3H, m), 7.95-8.05 (2H, m)

Reference Examples 64 - 66

By a similar manner to Reference Example 58, compounds shown in Table 10 were obtained.

[Table 10]

A-CH₂CH₂OH

Reference Example No	A	Yield (%)	Melting point	Recrystallization solvent
64		52	110-111	acetone - isopropyl ether
65		86	89 - 90	ether-isopropyl ether
66		88	58 - 59	isopropyl ether-hexane
67		87	47 - 48	hexane

Reference Example 68

By a similar manner to Reference Example 1, 2-(5-methyl-2-phenyl-4-oxazolymethoxy)-5-nitropyridine was obtained. Recrystallization from dichloromethane-isopropyl ether gave colorless prisms. Melting point: 142-143°C

Reference Example 69

By a similar manner to Reference Example 5, 5-amino-2-(5-methyl-2-phenyl-4-oxazolymethoxy)pyridine was obtained. Recrystallization from methanol-isopropyl ether gave colorless prisms. Melting point: 106-107°C.

Reference Example 70

To a solution of 5-amino-2-(5-methyl-2-phenyl-4-oxazolymethoxy)pyridine (7.10g) in acetone (200ml)-water (50ml) was added dropwise concentrated hydrochloric acid (7.46g) under ice cooling, and then solution of sodium nitrite (1.83g) in water (10ml) was added dropwise. The mixture was stirred for 10 minutes. To the mixture was added a solution of sodium iodide (4.40g) in water (20ml) under ice cooling. The mixture was stirred at 15 -20°C for 2 hours. To the reaction mixture was added water, and the mixture was neutralized with a solution of sodium hydrogen carbonate. The mixture was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water, dried over magnesium sulfate. The solvent was distilled off under reduced pressure and the residue was subjected to silica gel chromatography. From the fraction eluted with ethyl acetate-hexane (1:9, v/v), crystals (6.65g, 67%) of 5-iodo-2-(5-methyl-2-phenyl-4-oxazolymethoxy)pyridine were obtained. Recrystallization from ethyl acetate-hexane gave colorless prisms. Melting point: 129-130°C.

Elemental analysis (for C ₁₆ H ₁₃ IN ₂ O ₂)			
Calculated:	C, 49.00;	H, 3.34;	N, 7.14
Found :	C, 48.87;	H, 3.10;	N, 7.22

Reference Example 71

To a solution of 5-iodo-2-(5-methyl-2-phenyl-4-oxazolymethoxypyridine (6.53g) in tetrahydrofuran (60ml) was added dropwise a 1.6M solution of n. butyllithium in hexane (1.6M, 10.9ml) at -65°C, and the mixture was stirred for 20 minutes. N,N-dimethylformamide (2.43g) was added and temperature of the reaction mixture was elevated to room temperature. An aqueous solution of ammonium chloride was added to the mixture. The mixture was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried over magnesium sulfate. The solvent was distilled off under reduced pressure and the residue was subjected to silica gel chromatography. From the fraction eluted with ethyl acetate-hexane (1:3, v/v), crystals (2.80g, 57%) of 2-(5-methyl-2-phenyl-4-oxazolymethoxy)-5-pyridine carboxyaldehyde were obtained. Recrystallization from ethyl acetate-hexane gave colorless prisms. Melting point: 116-117°C

Elemental analysis (for C ₁₇ H ₁₄ N ₂ O ₃)			
Calculated:	C, 69.38;	H, 4.79;	N, 9.52
Found :	C, 69.47;	H, 4.75;	N, 9.60

Reference Example 72

By a similar manner to Reference Example 1, 2-[2-[5-methyl-2-(2-chlorophenyl)-4-oxazolyl]ethoxy]-5-nitropyridine was obtained. Recrystallization from ethyl acetate-ethyl ether gave pale yellow crystals. Melting point: 100-101°C

Reference Example 73

A mixture of 2-[2-[5-methyl-2-(2-chlorophenyl)-4-oxazolyl]ethoxy]-5-nitropyridine (1.69g), iron dust (787mg), acetic acid (25ml) and water (8ml) was stirred at 65-70°C for 3 hours. Insolubles were filtered off and the filtrate was evaporated under reduced pressure. To the residue was added water. The mixture was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried over magnesium sulfate. The solvent was distilled off, and the residue was subjected to silica gel chromatography. From the fraction eluted with methanol-chloroform (1:25, v/v), 5-amino-2-[2-[5-methyl-2-(2-chlorophenyl)-4-oxazolyl]ethoxy]pyridine (1.50g, 97%) was obtained.

NMR (δ ppm in CDCl₃): 2.36(3H,s), 2.99(2H,t,J = 6.7Hz), 4.48(2H,t,J = 6.7Hz), 6.59(1H,d,J = 8.6Hz), 7.03(1H,dd,J = 3.0&9.0Hz), 7.26-7.53(3H,m), 7.66(1H,d,J = 3.0Hz), 7.88-8.03(2H,m)

Reference Example 74

By a similar manner to Reference Example 9, 2-bromo-3-[2-[2-(2-chlorophenyl)-5-methyl-4-oxazolyl]ethoxy]-5-pyridyl]propionic acid methyl ester was obtained.

5 NMR (δ ppm in CDCl_3): 2.35(3H,s), 3.01(2H,t,J = 6.6Hz), 3.16(1H,dd,J = 7.3&14.5Hz), 3.37(1H,dd,J = 8.1&14.5Hz), 3.74(3H,s), 4.33(1H,dd,J = 7.3&8.1Hz), 4.56(2H,t,J = 6.6Hz), 6.67(1H,d,J = 8.4Hz), 7.26-7.51(4H,m), 7.87-8.03(2H,m)

Preparation Example 1

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Tablet production

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(1)	Compound obtained in Example 1	30 mg
(2)	Lactose	133.4 mg
(3)	Corn starch	30 mg
(4)	Hydroxypropyl cellulose	6 mg
(5)	Water	(0.03 ml)
(6)	Magnesium stearate	0.6 mg
		Total 200 mg

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Above components (1), (2), (3) and (4) were mixed and then kneaded with water, followed by vacuum drying at 40°C for 16 hours. The dry product was milled in a mortar and sieved through a 16-mesh sieve to yield granules. After component (6) was added, these granules were tableted, using a rotary tableting machine (produced by Kikusui Seisakusho), to yield 200 mg tablets.

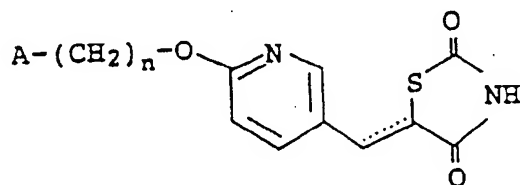
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Claims

1. Thiazolidinedione derivatives represented by the general formula (I):

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(I),

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wherein n represents an integer of from 1 to 3; A represents an aromatic 5-membered heterocyclic ring residue which has at least one nitrogen atom as a ring component atom, and which may be substituted, said residue (A) being bound within the alkoxy group $[\text{A}-(\text{CH}_2)_n-\text{O}-]$ via a carbon atom adjacent to a nitrogen atom of said residue and is a single bond or a double bond, and pharmacologically acceptable salts thereof.

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2. A compound as claimed in claim 1, wherein n is 2.

3. A compound as claimed in claim 1, wherein is a single bond.

4. A compound as claimed in claim 1, wherein is a double bond.

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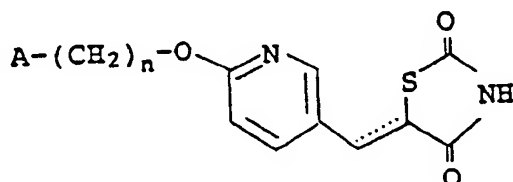
5. A compound as claimed in claim 1, wherein said compound is 5-[[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]methyl]-2,4-thiazolidinedione.

6. A compound as claimed in claim 1, wherein said compound is 5-[[2-[2-[5-methyl-2-(2-naphthyl)-4-oxazo-

yl]ethoxy]-5-pyridyl]methyl]-2,4-thiazolidinedione.

7. A compound as claimed in claim 1, wherein said compound is 5-[[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridyl]methylidene]-2,4-thiazolidinedione.

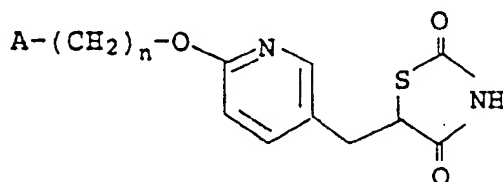
8. A pharmaceutical composition containing, as an active ingredient, a thiazolidinedione derivative represented by the general formula (I):



wherein n represents an integer of from 1 to 3; A represents an aromatic 5-membered heterocyclic ring residue which has at least one nitrogen atom as a ring component atom, and which may be substituted, said residue (A) being bound within the alkoxy group $[A-(CH_2)_n-O-]$ via a carbon atom adjacent to a nitrogen atom of said residue, and is a single bond or a double bond, or a pharmacologically acceptable salt thereof, together with one or more conventional pharmaceutically acceptable carriers, excipients, fillers or diluents, alone or in any acceptable combination, and/or together with one or more conventional pharmaceutically acceptable additives, alone or in any acceptable combination.

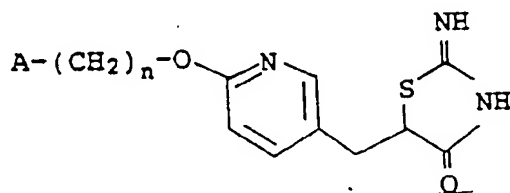
9. A pharmaceutical composition as claimed in claim 8, wherein said composition is a therapeutic agent for diabetes mellitus or hyperlipidemia.

10. A method of producing a thiazolidinedione derivative represented by the general formula (I-1):



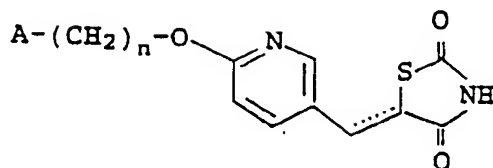
wherein n represents an integer of from 1 to 3; A represents an aromatic 5-membered heterocyclic ring residue which has at least one nitrogen atom as a ring component atom and which may be substituted, said residue (A) being bound within the alkoxy group $[A-(CH_2)_2-O-]$ via a carbon atom adjacent to a nitrogen atom of said residue,

characterised by the hydrolysis of an iminothiazolidinone compound represented by the general formula (II):



wherein the n and A symbols in said formula (II) have the same meanings as are given above in connection with formula (I-1).

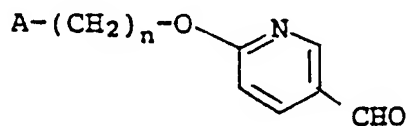
11. A method of producing a thiazolidinedione derivative represented by the general formula (I):



(I),

wherein n represents an integer of from 1 to 3; A represents an aromatic 5-membered heterocyclic ring residue which has at least one nitrogen atom as a ring component atom and which may be substituted, said residue A being bound within the alkoxy group $[A-(CH_2)_n-O-]$ via a carbon atom adjacent to a nitrogen atom of said residue, and is a single bond or a double bond,

characterised by the condensation of 2,4-thiazolidinedione with a compound represented by the general formula (III):



(III)

wherein the symbols n and A in said formula (III) have the same meanings as are given above in connection with formula (I), and, if necessary or desirable, by the reduction of the compound resulting from said condensation reaction.

12. The use of a compound (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as defined in claim 8, to prepare a medicine for the therapeutic treatment of diabetes mellitus.
13. The use of a compound (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as defined in claim 8, to prepare a medicine for the therapeutic treatment of hyperlipidemia.
14. The use of a compound (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as defined in claim 8, to prepare a medicine for the therapeutic treatment of hypertension.



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 93 31 0529

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL.5)
Y	CHEM. PHARM. BULL., vol.30, no.10, 1982 pages 3580 - 3600 T. SOHDA ET AL. * table VII, compounds 100,101; table IV, compounds 56,57 and 61-63 *	1-9, 12-14	C07D277/34 C07D277/20 C07D417/14 A61K31/44 A61K31/425
Y	CHEMICAL ABSTRACTS, vol. 117, no. 5, 3 August 1992, Columbus, Ohio, US; abstract no. 48397w, T. SOHDA ET AL * abstract * & J. MED. CHEM., vol.35, no.14, 1992 pages 2617 - 2626	1-9, 12-14	
Y	EP-A-0 332 332 (PFIZER INC.) * abstract; examples 18,19 *	1-9, 12-14	
A,D	DATABASE WPI Week 8026, Derwent Publications Ltd., London, GB; AN 80-45607C & JP-B-62 057 635 (TAKEDA CHEMICAL IND. KK.) * abstract *	1-9, 12-14	TECHNICAL FIELDS SEARCHED (Int. CL.5) C07D A61K
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 19 April 1994	Examiner Frelon, D
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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